A MILD NON-CLASSIC FORM OF BCS1L RELATED MITOPATHY MIMICKING FATTY ACID B OXIDATION DISORDER: CASE REPORT AND REVIEW OF LITERATURE

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INTRODUCTION

BCSL1 mitopathies are the commonest form of complex III disorder and are part of the oxidative phosphorylation disorders. Although classical phenotypes associated with biallelic variants in BCS1L are described (Bjornstad syndrome; GRACILE syndrome; Complex III deficiency, nuclear type 1; Nuclear Leigh Syndrome Spectrum) literature reports evidence a phenotype continuum with many intermediary forms. We describe a case of a 6-year-old boy with a mild form of disease with 3 pathogenic variants on BCS1L gene.

CASE REPORT

Boy, 6 years old, was referred to the clinical genetics service due to recurrent hypoglycemia, nausea and vomiting associated with metabolic acidosis onset at age 1. He presented with development delay and learning difficulties . Heart evaluation was normal. Amino acid chromatography evidence no alterations, but acylcarnitine profile evidenced low free carnitine and elevated C10, C12:1 C14, C14:1, C14:2, C16 and C16:1. Urine organic acid evidence elevated lactic acid, 3-OH-butyric acid, 2-OH-butyric acid and 4-OH-phenyl-lactic acid. The patient was treated with L-carnitine and cornstarch with a good metabolic response. Whole Genome Sequence evidenced 3 variants in compound heterozygous in BCSL1 (c.355C>T:p.(Arg119Ter); c.147A>G:p.(?); c.164C>G:p.(?)), all pathogenic.

Table 1: Differential diagnosis of hypoglycemia

Feature / Disorder	Complex III deficiency (BCS1 L-related)	Glutaric aciduria type II (MADD)	β-oxidation defects
Hypoglycemia (ketotic vs non-ketotic)	Variable/Non specific.	Typically non-ketotic hypoglycemia	Typically non-ketotic hypoglycemia
Acylcarnitine profile (plasma)	Usually non-specific; may be normal or show secondary, variable changes; no pathognomonic pattern	Characteristic broad elevation of C4, C5 and C8. Other higher acylcarnitine may be elevated	Defect-specific patterns: • MCAD → ↑ medium-chain (C8 ± C6, C10) • VLCAD / LCHAD → ↑ long-chain (C14:1, C16)
Acidosis	Lactic Acidosis	Organic metabolic acidosis	Lactic acidosis

DISCUSSION AND CLOSING COMMENTS

We describe a mild atypical form of BCS1L-related disorder presenting with recurrent hypoglycemia and metabolic acidosis responsive to L-carnitine and cornstarch. Clinical features of atypical forms of the disease can mimic other inborn errors of metabolism, including fatty acid B-oxidation defects. Although genotype-phenotype correlation of BCS1L related disorders is limited, prognosis correlates with age onset of presentation of symptoms, with early death occurring when symptoms start in the first month of life. The unknown phase of the variant limits genotype-phenotype correlation in our patient and new evidence is necessary to determine if L carnitine can prevent progression of the disease in the future. The mitochondrial role in energy production and related proteins explain the clinical overlap between the symptoms of BCS1L and other inborn errors of metabolism like fatty acid B oxidation defect, glycogen storage diseases, organic acidemia and other OXPHOS disorders. Disorders of oxidative phosphorylation present a highly variable phenotype with intermediary forms along the phenotype spectrum. The intermediary forms of the disease should be suspected in clinical cases resembling fatty acid B oxidation defects and organic aciduria due to overlapping clinical features. Next Generation Sequencing is an essential tool for the diagnosis of this rare metabolic disorder and doesn't have any change with the diet.

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